Studies on delirium and associated cognitive and functional decline in older surgical patients

Beishuizen, Sara

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Chapter 4

The effect of treatment of anemia with blood transfusion on delirium: a systematic review

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Vera van der Zanden

Sara J. Beishuizen

Lieke M. Swart

Sophia E. de Rooij

Barbara C. van Munster

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ABSTRACT

Background: Treating the precipitating factors of delirium is the mainstay of the prevention and treatment of delirium. We aim to investigate the role of anemia and blood transfusion within the multicomponent prevention and treatment strategy of delirium.

Design: Systematic review

Setting, participants and measurements: We searched MEDLINE from 1946 till November 2014 and included studies that were about blood transfusion, as treatment strategy of delirium or as risk factor, and had delirium as outcome. Quality assessment was based on form III of the Dutch Cochrane institute for assessment of a cohort study.

Results: We included 23 studies (n=29,471). The majority of the studies (n=22) had a limited quality and for one study quality was uncertain. Two studies evaluated the association between transfusion strategy and postoperative delirium and found no association. Twenty-one studies investigated blood transfusion as a risk factor for delirium. In four of the 21 studies it could be assumed that delirium occurred after transfusion. One of these studies stated that transfusion was a significant risk factor for subsequent delirium (Odds ratio(OR)=3.68, 95% confidence interval(CI)=1.32-10.94). The other three studies found no association between transfusion and delirium. In the remaining 17 studies, it was not clear whether delirium occurred before or after transfusion, so no conclusion could be drawn on the role of transfusion in delirium development.

Conclusion: The majority of the included studies was not suited to answer the research question properly as the time course of the beginning of delirium as to transfusion was lacking. Our review shows that there is no good quality evidence available for blood transfusion to be a risk factor for delirium or to be a preventive or treatment option.

BACKGROUND

Delirium has a high prevalence (18-37% in The Netherlands) in hospitalized patients and is associated with a higher risk of complications.[1] Delirium is associated with more hospital-acquired complications, such as falling, more frequent admission to long-term care, increased length of hospital stay, cognitive and functional impairment, institutionalization and mortality.[2] By reducing the incidence, duration, or severity of delirium, negative sequels for the patient can be prevented and health care related costs reduced.[1]

Delirium has by definition a somatic underlying cause, but frequently there is a combination of precipitating factors. The main purpose of prevention and treatment of delirium consists of minimizing these underlying factors - in a multicomponent approach.[1] Since anemia is one of the precipitating factors, correction of anemia is part of the multicomponent prevention and treatment strategy of delirium.[3-6]

The quickest way to treat anemia is blood transfusion, although a transfusion might cause several unwanted effects such as circulatory overload, allergic reactions, synthesis of antibodies, viral transmission, bacterial contamination, and hemolytic transfusion reactions.[7] Therefore, there should be a good indication for transfusion. The effect of blood transfusion is not only dependent on hemoglobin level, but also on other clinical factors that play a role in the balance between oxygen supply and demand. These factors should be taken into account in the decision to transfuse or not.[8] When transfusion is given in a controlled environment, complications as volume overload can be prevented with actions like, identification of patients at risk, slowing down the infusion speed, and carefully monitoring the patient (mainly the changes in blood pressure).[9]

Also, transfusion in itself could be related to delirium.[4] A hypothesis is that delirium can be triggered by an acute inflammatory response, which can be induced by blood transfusion.[10] Blood transfusion can cause higher concentrations of cytokines in the circulating blood [11], it can amplify the systemic inflammatory reaction caused by surgery [12], and it can cause a systemic inflammatory response syndrome.[13] A systemic inflammatory reaction can be passed on to the brain by different mechanisms. The idea is that delirium can arise when there is a combination of neuroinflammation and a reduced functional reserve of the brain.[14]

According to the Dutch blood transfusion guideline of 2011, patients with acute normovolemic anemia should receive a transfusion if the hemoglobin value (Hb) is < 8.1 g/dL in healthy elderly (> 60 years) or < 9.7 g/dL in elderly patients with comorbidity. Comorbidity is limited to: not able to increase necessary cardiac output, septic and toxic patients, or patients with serious lung disease, symptomatic cerebrovascular disease, or in a systemic condition which causes a constant life threatening situation. Delirium is not described as an indication.[7] Blood transfusion guidelines from other countries, like the guideline of the 'American Society of Hematology' [15], from the 'British Committee for Standards in Haematology'[16], and from the 'American Association of Blood Banks'[17] also do not describe delirium as an indication for transfusion. Delirium guidelines, like the guidelines of the 'Nederlandse Vereniging voor Klinische Geriatrie'[1] and the 'American Geriatrics Society' [18] also do not describe it as indication. In the delirium guideline of the 'National Institute for Health and Care Excellence' (NICE)[2] there is a short remark on giving blood transfusion to keep hematocrit above 30% and to maintain adequate oxygen delivery as part of a multicomponent intervention to prevent delirium, but the exact role of transfusion is not specifically mentioned.

Anemia is however a precipitating factor for post-operative delirium and therefore treating patients without the above described comorbidity but with a delirium and Hb below 9.7 g/dL could be defended.[3] However, this approach is not evidence based and could also aggravate delirium for the reasons stated above. Because it is not clear if transfusion helps to prevent or resolve delirium, or if it is one of the causes for it, physicians struggle in daily practice with the dilemma whether to give or to not to give a transfusion in the treatment of patients with anemia and (high risk for) delirium.

In order to gain a better insight into the effects of treatment of anemia, especially blood transfusion, as a distinct part of the multifactorial prevention and treatment strategy of delirium, we performed a systematic review to search for studies on the effects of blood transfusion in delirium.

METHODS

Search strategy

We searched MEDLINE for articles published from 1946 until November 2014. We used a search strategy combining search terms retrieved from relevant Cochrane reviews on delirium[19], anemia and treatment of anemia[20] (see Supplemental Appendix 1 for search strategy). After study selection, references of eight included publications, Lin[4], Koster[21], Whitlock[22], Balasundaram[23], Beliaev[24], Fan[25], Gruber-Baldini[26], and Vochteloo[27], were cross-referenced to retrieve any additional relevant citations.

Study selection

Based on title and abstract, we checked all articles on relevance, language, and study type. We included articles in English, Dutch, and German. We included all studies that investigated risk factors for delirium, to be sure not to miss relevant studies on anemia and blood transfusion.

After the first selection on title and abstract, one person screened the full articles. We included cohort studies that considered blood transfusion in the treatment strategy of delirium or as risk factor, and all had delirium as outcome.

Based on title and abstract, we excluded studies concerning delirium tremens or alcohol withdrawal delirium and studies without original data, like systematic reviews. With full text screening, we excluded studies with participants with a mean age below 55 years old and studies which did not mention age. If there was doubt in the selection process, the opinion of a second reviewer was asked.

Quality assessment

Quality assessment was based on form III of the Dutch Cochrane Institute for assessment of a cohort study. There were nine questions that had to be answered for each study:

1. Are the study groups well defined?
2. Can selection bias be adequately excluded?
3. Is the exposition well defined and was the method of examination of the exposition adequate?
4. Is the outcome well defined and was the method of examination of the outcome adequate?
5. Was the outcome defined blinded before knowledge of the exposition?

6. Was the follow-up good?
7. Can selective loss-to-follow-up be adequately excluded?
8. Were the most important confounders or prognostic factors known and taken into account in study design or analysis?
9. Are the results of this study valid and applicable?

Exposition was defined as 'blood transfusion' and outcome as 'delirium'. Exposition was adequately described when it was clear what was meant by transfusion (for example transfusion yes/no or transfusion of more than 1000 mL) and when the timing of transfusion with respect to delirium assessment was clearly described. Diagnosis of delirium was esteemed adequate if it was based on the Confusion Assessment Method (CAM) or DSM-IV criteria for delirium.[1] Follow-up was adequate when length of follow-up was at least until day five postoperative or during whole hospital stay and delirium was assessed before transfusion. Surgery, intra- and postoperative hemoglobin levels and blood loss were judged to be imported confounders that had to be taken into account in the analysis.

Question 9 was answered as follows; study quality got rated as good when none of the eight questions were answered with 'no', study quality got rated as limited when relevant confounders were not taken into account and/or when delirium was not assessed with an adequate method.

For Randomized Controlled Trials (RCTs) we did an extensive quality assessment with a form of the Dutch Cochrane Institute for RCTs.

Quality assessment was performed by two persons independently and consensus was achieved through discussion.

Data extraction

We collected information from the studies on study design, country, type of patients (surgical/medical, kind of surgery), number of patients, mean age, sex, preoperative or pre-transfusion hemoglobin levels, transfusion strategy, delirium assessment method, timing of delirium assessment, incidence of delirium, reported odds ratios (OR) for delirium on transfusion from univariate and multivariate analysis, and factors controlled for in multivariate analysis. In case OR's and 95% Confidence Intervals (CI) were not reported by the author, OR were calculated using cross tabulation and significance was mentioned, based on reported P-values.

RESULTS

Identification of studies

We found 225 studies of which 140 studies were excluded based on relevance, 39 based on language and four based on type of data after screening on title and abstract. After full text screening, we included 23 studies. 16 more studies were excluded based on relevance, and three based on age (Figure 1). Screening of reference lists of other articles did not yield extra results.

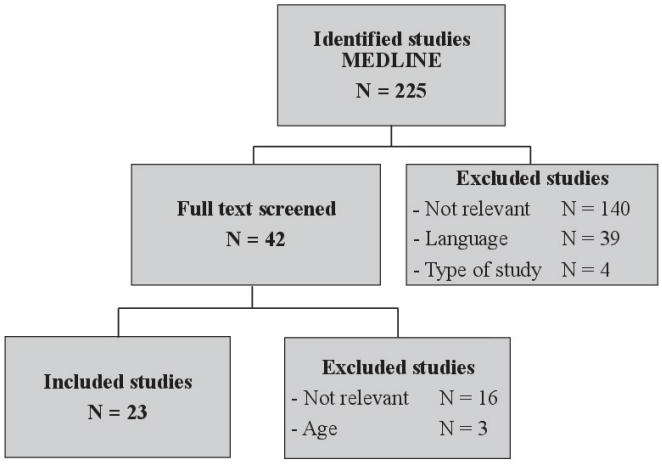

Figure 1. Flowchart of study selection

Characteristic of the included studies

Table 1 shows the characteristics of the 23 included studies. Total number of included patients was 29,471. The majority of the included studies consist of small studies, the number of included patients ranged from 38 to 16,184. Mean age ranged from 58.2 to 83.6 years old. Most studies (N = 21) were cohort studies, fifteen prospective[10,25,28-40], six retrospective[24,41-45], and one partly prospective and partly retrospective.[27] Two studies were (part of) a randomized controlled trial.[25,26] Twenty-one studies investigated blood transfusion as a risk factor for delirium and two studies evaluated the association between different transfusion strategies and delirium incidence.[25,26] Blood transfusion was given when hemoglobin fell below 8 g/dL in the restrictive strategy group and below 10 g/dL in the liberal strategy group in both studies. No studies that specifically investigated transfusion as part of delirium treatment were found.

All studies included surgery patients, twelve studies non-cardiac surgery[10,25-27,33,34,38,39,41-44], ten cardiac surgery[28-32,35-37,40,45], and one study both non-cardiac surgery (69%) and medical patients (31%) with severe anemia.[24]

In the studies that looked at transfusion as risk factor, transfusion strategy was well described by Beliaev [24] and Vochteloo[27]. Transfusion indications in Beliaev's study[24] were: hemorrhagic shock, ongoing bleeding with hemodynamic instability, Hb ≤ 7.0 g/dl, Hb 7.01–8.0 g/dl with exercise intolerance, Hb 7.01 –8.0 g/dl with Auckland AMRS ≥4, Hb 8.01–10.0 g/dl with acute myocardial ischemia, or Hb 8.01–10.0 g/dl with neutropenic sepsis. Vochteloo's[27] indications were: a hemoglobin level below 8.0 g/dL in the general population or 9.7 g/dL in patients with a serious cardiac condition or symptomatic anemia.

Delirium incidence ranged from 3% to 48%. Delirium was assessed by the Confusion Assessment Method in nine studies[10,25,26,32-34,37,38,41], the DSM criteria for delirium in five studies[27,28,30,31,36], one study used both methods[42], seven studies used no validated method[29,35,39,40,43-45], and one study did not mention which method was used.

The exact timing and frequency of delirium assessments was not well described. In four studies, Behrends[10], Kawaguchi[41], Lee[42], and Sasajima[38], delirium was diagnosed after transfusion and was not present before surgery as patients with an pre-operative delirium were excluded and transfusion was performed during surgery. In the other studies delirium was not excluded prior to transfusion, so it was not clear whether delirium occurred before or after transfusion. Table 2 shows the timing of delirium assessment and transfusion of each included study, as far as it could be retrieved from the article texts.

Quality of the included studies

All studies but one (N = 22) had a limited quality and for one study (Behrends[10]) the quality was uncertain. There were no studies with good quality. The main reason for the limited quality was that most studies (N = 22) did not take relevant confounders into account in their analysis. Another weak point was that the indication and timing of transfusion were unclear and that the transfusion strategy was not stated in most studies.

Also, presence of delirium was not always assessed with a valid method and it was also often not known if it was performed blinded to knowledge on transfusion status. For most studies, it was

unknown if the follow-up was adequate and if selective loss-to-follow up could be adequately excluded. Main reasons were that loss-to-follow was not described at all and if loss-to-follow up was described, it was unknown to which group drop-outs belonged.

Positive points were that almost all studies had well-defined study groups, and that selection bias could almost always be excluded. See Supplemental Table 1 for the table of quality assessment per study.

The quality of Gruber-Baldini's[26] and Fan's[25] study was additionally assessed with a form from the Dutch Cochrane Institute for RCTs. In the study of Gruber-Baldini[26], the intervention was randomized by central telephone randomization system. Patients, physicians and study personnel were not blinded. The study groups were not entirely comparable, but this was adjusted for in the analysis. It is not known if the patients were treated in the same way (except from transfusion strategy).

In Fan's[25] study, the intervention was randomized by a random number table and a sealed envelope technique. It is unknown if patients, physicians and study personnel were blinded. The study groups were comparable at the start of the trial. The patients were not entirely treated in the same way; besides the differences in transfusion strategy between the study groups, patients in the restrictive transfusion group received more volume of Ringer's lactate solution and hydroxyethyl starch.

This extensive quality check did not change our opinion on these studies based on the other quality check. Our main concern stays the same: They both do not report when the transfusion(s) is/are actually given in relation to the onset of delirium.

Findings of the included studies

Table 3 shows the reported odds ratios (OR) of the included studies. In four studies, Behrends[10], Kawaguchi[41], Lee[42], and Sasajima[38], it could be assumed that delirium occurred after transfusion as delirium prior to surgery was an exclusion criterion and transfusion was performed during surgery. Behrends[10] performed a multivariate analysis and reported intraoperative blood transfusion of ≥ 1000 ml as a statistical significant risk factor for subsequent delirium (Odds Ratio (OR) = 3.68, 95% Confidence Interval (CI) = 1.32-10.94). The other three studies only performed univariate analysis and found no association between transfusion and delirium.

Of the seventeen studies in which the timing of transfusion compared to delirium assessment was not clearly described, twelve studies reported their results from univariate analysis. Eleven of these studies concluded that blood transfusion was a statistical significant risk factor for delirium. Gokgoz[29] reported no p-value or CI. Nine of the seventeen studies performed a multivariate analysis, eight of them reported that transfusion was independently associated with delirium, ORs varied between 1.15 to 4.59. Beliaev[24] found that blood transfusion had a significant protective effect (OR = 0.34, 95% CI = 0.13–0.90).

Fan[25] and Gruber-Baldini[26] investigated a liberal versus a restrictive transfusion strategy, both reported that the transfusion strategy was not associated with postoperative delirium.

Table 1. Characteristics of the Included Studies

Study (author year)	Study design	Population	Number of patients	Mean age ± SD (years)	Sex N = male (%)	Delirium assessment	Delirium incidence (%)	Mean preoperative hemoglobin level/SD (g/dL)
Behrends[10]	Prospective study	Major non-cardiac surgery	472	≥ 65[a]	?	CAM	137 (29.0)	?
Beliaev 2012[24]	Multicenter, retrospective study	Non-cardiac surgery and 31.1% medical patients	206	62.1	89 (43.2)	?	22 (10.7)	?
Bucerius 2004[28]	Prospective study	Cardiac surgery	16184	64.8 ± 10.4	11522 (71.2)	DSM III	1354 (8.4)	?
Fan 2014[25]	RCT	Orthopedic surgery	186	74.0	63 (33.9)	CAM-ICU	42 (22.6)	11.9
Gokgoz 1997[29]	Prospective study	Cardiac surgery (NYHA class II-b)	50	61 ± 13	32 (64.0)	STAI-T, MMSE and/ or SPECT rCBF	6 (12)	?
Gruber-Baldini 2013[26]	Ancillary study to a RCT	Cardio- vascular patients undergoing hip fracture surgery with hemoglobin <10 g/dL within 3 days of surgery	139	81.5 ± 9.1	37 (26.8)	CAM	?	11.9

Study (author year)	Study design	Population	Number of patients	Mean age ± SD (years)	Sex N = male (%)	Delirium assessment	Delirium incidence (%)	Mean preoperative hemoglobin level/SD (g/dL)
Kawaguchi 2006[41]	Retrospective study	Spine surgery	104	59.2	186 (54.6)	CAM	13 (3.8)	12.5
Kazmierski 2010[30]	Prospective study	Cardiac surgery	563	62 ± 9.0	395 (70)	DSM-IV	92 (16.3)	?
Krzych 2013[31]	Prospective study	Cardiac surgery	5781	62.8 ± 9.9	4031 (69.7)	DSM-IV	236 (4.1)	13.7 ± 1.6
Lee 2010[42]	Retrospective study	Spine surgery	81	73.5	28 (34.6)	DSM-IV and CAM	11 (13.6)	12.5
Lescot 2013[43]	Retrospective study	ICU patients with liver transplantation	281	58.2	?	No validated methods	28 (10.0)	?
Li 2014[32]	Prospective study	Cardiac surgery	38	62.4 ± 11.8	34 (89.5)	CAM	7 (18.4)	?
Marcantonio 1998[33]	Prospective study	Major non- cardiac surgery	1341	67 ± 9	603 (45)	CAM, medical records, nursing intensity index	117 (9)	?
Mardani 2012[45]	Retrospective study	Cardiac surgery	196	61.9	183 (93.4)	DSM-IV when MMSE ≤23	34 (17.3)	?

Study (author year)	Study design	Population	Number of patients	Mean age ± SD (years)	Sex N = male (%)	Delirium assessment	Delirium incidence (%)	Mean preoperative hemoglobin level/SD (g/dL)
McAlpine 2008[34]	Prospective study	Major surgery for suspected gynecologic cancers	103	72	0 (0)	CAM	18 (17.5)	?
Norkiene 2007[36]	Prospective study	Cardiac surgery	1367	65.0	1035 (75.7)	DSM-IV	42 (3.1)	?
Norkiene 2013[35]	Prospective study	Cardiac surgery	87	65.1	?	ICDSC	12 (13.3)	?
Roggenbach 2014[37]	Prospective study	Cardiac surgery	92	67.5 ± 8.9	66 (60.6)	CAM-ICU	44 (47.8)	13.2 ± 1.6
Sasajima 2000[38]	Prospective study	Elective bypass surgery for chronic lower limb ischemia	110	71.6 ± 6.6	101 (91.8)	CAM	32 (29.1)	?
Schneider 2002[39]	Prospective study	Elective surgery > 90 min	47	66.8 ± 7.1	38 (80.9)	DSM IV criteria after surgery, DRS daily	17 (36.2)	13.9
Stransky 2011[40]	Prospective study	Cardiac surgery	455	66.8	341 (74.9)	ICDSC, BPS and RASS	42 (9.2)	12.5

Study (author year)	Study design	Population	Number of patients	Mean age ± SD (years)	Sex N = male (%)	Delirium assessment	Delirium incidence (%)	Mean preoperative hemoglobin level/SD (g/dL)
Vochteloo 2011[27]	Retrospective (2005-2007) and prospective (2008-2009) study	Hip fracture surgery	1262	83.6 ±7.1	330 (26.1)	DSM-IV	317 (25.1)	12.4 ± 1.6
Yamagata 2005[44]	Retrospective study	Head and neck cancer surgery	38	59.2	29 (76.3)	Confusion after surgery that interfered with post-operative recovery	10 (26.3)	?

[a] Mean age unknown, ?: Unknown, BPS: Behavioral Pain Scale; CAM: confusion assessment method; DRS: Delirium Rating Scale; DSM: Diagnostic and Statistical Manual of Mental Disorders; ICU: Intensive Care Unit; ICDSC: Intensive Care Delirium Screening Checklist; MMSE: Mini mental state examination; POD: Postoperative day; RASS: Richmond Agitation and Sedation Scale; RCT: Randomized Controlled Trial.

Table 2. Timing of Delirium Assessment and Transfusion of Each Included Study

Study (author and year)	Timing of transfusion	Pre-operative delirium excluded	Pre-transfusion delirium excluded	Post-operative delirium assessment	Post-transfusion delirium assessment
Behrends 2013[1]	Intraoperative	+	+[a]	+	+[b]
Beliaev 2012[24]	Unknown	? [c]	-	? ‡	+
Bucerius 2004[28]	Perioperative	-	-	+	?
Fan 2014[25]	Perioperative	+	-	+	?
Gokgoz 1997[29]	Postoperative	+	-	+	?
Gruber-Baldini 2013[26]	Postoperative	-	-	+	?
Kawaguchi 2006[41]	Intraoperative	+	+[a]	+	+[b]
Kazmierski 2010[30]	Postoperative	+	-	+	?
Krzych 2013[31]	Perioperative	-	-	+	?
Lee 2010[42]	Intraoperative	+	+[a]	+	+[b]
Lescot 2013[43]	Intraoperative	-	-	+	+[b]
Li 2014[25]	Perioperative	+	-	+	?
Marcantonio 1998[33]	Perioperative	-	-	+	?
Mardani 2012[45]	Unknown	-	-	+	?
McAlpine 2008[34]	Postoperative	-	-	+	?
Norkiene 2007[36]	Postoperative	-	-	+	?
Norkiene 2013[35]	Postoperative	-	-	+	?

Study (author and year)	Timing of transfusion	Pre-operative delirium excluded	Pre-transfusion delirium excluded	Post-operative delirium assessment	Post-transfusion delirium assessment
Roggenbach 2014[37]	Intraoperative	-	-	+	+[b]
Sasajima 2000[38]	Intraoperative	+	+[a]	+	+[b]
Schneider 2002[39]	Postoperative	-	-	+	?
Stransky 2011[40]	Postoperative	-	-	+	?
Vochteloo 2011[27]	Postoperative	?	-	+	?
Yamagata 2005[44]	Intraoperative	-	-	+	+[b]

[a] Pre-transfusion data are the same as preoperative data. [b] Post-transfusion data are the same as post-operative data. [c] 31% Of the patients did not have surgery

Table 3. Transfusion as Prognostic Factor for Delirium

Study (author and year)	Prognostic factor	Univariate analysis (OR (95% CI))	Multivariate analysis (OR (95% CI))	Factors included in multivariate analysis
Studies in which it was clear that delirium was absent before surgery and diagnosed after transfusion				
Behrends 2013[10]	Intraoperative blood transfusion ≥1000 mL	3.18 (1.68-6.00)	3.68 (1.32-10.94)	Age, sex, TICS score, history of central nervous system (CNS) disorder, alcohol use, chronic narcotic use, preoperative hemoglobin and creatinine concentrations, American Society of Anesthesiologists class, blood loss, length of surgery, surgical risk group
Kawaguchi 2006[41]	Intraoperative transfusion	1.41[a] ns	NR	Not applicable
Lee 2010[42]	Intraoperative transfusion	0.36 [a] ns	NR	Not applicable
Sasajima 2000[38]	Intraoperative blood transfusion	2.27 [a] ns	NR	Not applicable
Studies in which the timing of transfusion as to delirium assessment was not exactly known				
Beliaev 2012[b24]	Blood transfusion	NR	0.34 (0.13-0.90)	Age, European ethnicity, Maori ethnicity, diabetes mellitus, bronchiectasis/tuberculosis, acute/chronic renal failure
Bucerius 2004[28]	Red blood cell (RBC) transfusion ≥2000 mL	4.72 [a] s	3.15 (2.71–3.65)	History of cerebrovascular disease, atrial fibrillation, diabetes mellitus, peripheral vascular disease, left ventricular ejection fraction ≤ 30%, preoperative cardiogenic shock, urgent operation, operating time ≥ 3h

Study (author and year)	Prognostic factor	Univariate analysis (OR (95% CI))	Multivariate analysis (OR (95% CI))	Factors included in multivariate analysis
				intraoperative hemofiltration, beating-heart surgery, age
Gokgoz 1997[29]	Transfusion of blood or blood products ≥7 packs	6.83 [a]	NR	Not applicable
Kazmierski 2010[30]	Postoperative RBC transfusion >4 units	4.04 (2.23–7.31)	NR	Not applicable
Krzych 2013[31]	Any blood transfusion (perioperative)	4.65 (3.53–6.13)	4.17 (2.42–7.21)	Postoperative cerebral ischemia, age > 65 years, carotid artery stenosis, urgent and emergent mode of surgery, hypertension, fasting glucose level, intraoperative fluctuation of arterial oxygen partial pressure, intraoperative fluctuation of hematocrit
Lescot 2013[43]	Intraoperative Packed RBC (per PRBC unit increase)	NR	1.15 (1.01–1.18)	Encephalopathy ≥ grade 2, renal replacement therapy, Apache II score
Li 2014[32]	Intra- and postoperative transfusion	36.82 [a,c] s	NR	Not applicable
Marcantonio 1998[33]	Blood transfusion (odds ratio per unit)	1.3 (1.2–1.4)	NR	Not applicable
Mardani 2012[45]	Packed Cells > 4 units	4.63 (1.35-15.80)	NR	Not applicable
McAlpine 2008[34]	Postoperative transfusion	7.68 [a] s	NR	Not applicable

Study (author and year)	Prognostic factor	Univariate analysis (OR (95% CI))	Multivariate analysis (OR (95% CI))	Factors included in multivariate analysis
Norkiene 2007[36]	Postoperative RBC transfusion	4.58 [a] s	4.59 (2.10-10.06)	Emergency surgery, duration of operation, retrograde cardioplegia, ICU stay, low cardiac output syndrome, postoperative intra-aortic balloon pump, atrial fibrillation, perioperative myocardial infarction, inotropes for more than 12 hours, controlled mechanical ventilation duration, mortality
Norkiene 2013[35]	Postoperative RBC transfusion (units)	1.99 (1.20–3.31)	NR	Not applicable
Roggenbach 2014[37]	Intraoperative blood transfusion	NR	1.55 (1.03-2.32)	Age, smoking, albumin, hemoglobin, postoperative intubation time, time spent in intensive and intermediate care unit, apnea-hypopnea index (AHI), mean oxygen desaturation
Schneider 2002[39]	Perioperative transfusion (ml)	NR	b[d]: 0.0005	Preoperative depression scores, cognitive dysfunction
Stransky 2011[40]	Units of PRBCs (perioperative)	1.20 (1.08-1.34)	1.18 (1.05-1.34)	Age, depression, diuretics preoperative, duration of aortic clamping, bètablocker preoperative, higher hemoglobin before surgery (g/dL)
Vochteloo 2011[27]	Allogenic blood transfusion (perioperative)	NR	1.67 (1.28-2.20)	Age, gender, American Society of Anesthesiologists (ASA), type of fracture, and type of anesthesia

Study (author and year)	Prognostic factor	Univariate analysis (OR (95% CI))	Multivariate analysis (OR (95% CI))	Factors included in multivariate analysis
Yamagata 2005[44]	Intraoperative blood transfusion >4 units	7.00 [a] s	NR	Not applicable
Studies comparing a liberal versus a restrictive transfusion strategy				
Fan 2014[25]	Liberal transfusion strategy	1.16 [a] ns	NR	Not applicable
Gruber-Baldini 2013[26]	Liberal transfusion strategy	RR: 1.26 (0.76–2.08)	NR	Not applicable

[a] Odds-ratio calculated by ourselves, [b] Study population includes 31% medical patients, [c] One of the groups contained 0 patients, so we added 0.5 to each group to calculate the odds ratio, [d] b: parameter estimates. CI: confidence interval, NR: not reported, ns: not significant (reported in the article), OR: Odds ratio, s: significant (reported in the article).

DISCUSSION

Most studies found that perioperative blood transfusion might be associated with perioperative delirium. Nonetheless, the designs of the included studies were not suited to answer the research question properly.

Only Behrends and colleagues[10] both attempted to rule out the onset of delirium before transfusion and corrected for relevant confounders in their analysis. However, the relatively short follow-up prevents us from drawing strong conclusions. Therefore the question whether transfusion should be used in order to prevent or resolve delirium or might even lead to delirium remains unsolved.

These results are not in line with our prior expectations and the prevailing guidelines. Before we conducted this study we expected transfusion to be effective in de multicomponent prevention and treatment strategy of delirium despite its adverse effects, since anemia is a precipitating factor for delirium[3,4] and transfusion can correct anemia.

The general lack of quality of the identified studies in our review is the main reason for our conflicting findings. First of all, in most studies it was not clear if delirium assessment was done before or after transfusion. The exact timing of both delirium onset and transfusion have been built in uncertainty, and therefore it may be difficult to sort out sequencing (which came first?). Delirium is usually assessed on a daily basis in most studies, because the precise timing of its onset is very difficult to ascertain. Transfusion itself is often administered over several hours. However, it remains very important to know the sequencing to draw conclusions. In most included studies it could very well have been possible that delirium was already present before transfusion with anemia as precipitating factor. But, even if delirium was diagnosed after transfusion, it cannot be stated that transfusion was the cause of delirium, because there are multiple perioperative confounding factors, like severity of illness (APACHE II score), medical restraints, and infections, that could also play a role in the development of delirium.[1] In most studies, relevant confounders were not taken into account. Also, the rules governing transfusion were not mentioned in most included studies. Therefore there is a lack of standardization of the transfusion rules.

Delirium incidence was surprisingly low in the included studies, which might have been caused by under diagnosis because of the assessment method used.[1] Delirium incidence ranged from 3% to 48%. In a surgical population one would expect the delirium incidence to be higher, 37-46% (range 10-60%) in a general surgery population and 50-67% in a patients who underwent cardiotomy.[46] In total, seven studies used no validated methods to diagnose delirium and for one study delirium assessment was not described. Seven of this eight studies reported an incidence which was lower than expected, only Schneider[39] reported an incidence which was in the range of expectance. Another point is, the two RCTs of different types of transfusion strategies[25,26] only address single component intervention. Lack of effectiveness in this context does not rule out a role for transfusion as part of a multi-component strategy, which has generally proven more effective for delirium prevention.[1]

Because most of the included studies had a mean age around 60 years old, it is unknown if the results can be extrapolated to often geriatric patients of a higher age, 80 years and above. Also, the included population consists almost completely of surgical patients. None of the included studies provided information on pre-hospitalization hemoglobin levels. Consequently anemia is studied here as a result of blood loss after the initiating event or from surgery, and is not a persistent anemia. Therefore, the results of our study may not be applicable to medical patients.

Strengths and limitations of the review

There are some limitations of this review that are worth mentioning. The first one is that we only searched for studies in MEDLINE, so we might have missed relevant articles that were not indexed for MEDLINE. We were also not able to include studies with languages other than English, Dutch, and German.

Also, we were not able to perform a subgroup analysis for elective and emergency surgery patients because of the lack of information provided in the original articles. Of course, emergency surgery patients are at higher risk for delirium, so this could have influenced the results. Because of the clinical heterogeneity in population, delirium assessment, transfusion strategy and study design, we have not performed a meta-analysis.

One of the strengths of our review is that we performed a sensitive MEDLINE search, which makes it unlikely that we have missed relevant studies in MEDLINE with this search. Another strength is that we used liberal inclusion criteria and included all relevant studies that mentioned

blood transfusion in relation to delirium. Because of this, our review gives a good overview of the present literature on this subject. Such an overview did not exist yet and identifies the gap in literature on this subject clearly. We did an extensive quality check of the included studies and tried to present the timing of transfusion and delirium as good as possible to be able to show the most accurate relationship between delirium and transfusion.

CONCLUSION

Most included studies claimed that blood transfusion was associated with delirium. However, the included studies were not suited to answer our complete research question properly because of methodological issues. Our review shows that there is no good quality evidence available for blood transfusion to be a risk factor for delirium or to be a preventive or treatment option. Therefore, it is still unclear how to deal with delirium and blood transfusion in clinical practice. We know currently too little about the role of blood transfusion in delirium to take delirium into account in the transfusion decision yet. Therefore we advise physicians to follow their transfusion guideline until evidence on delirium and blood transfusion is available.

More research is necessary to find out what the role of blood transfusion in delirium management should be. For a single component treatment in a homogeneous population a randomize controlled trial (RCT) would be ideal. However, a RCT might not be ethical because of the lacking indication that blood transfusion would be beneficial in preventing delirium combined with the possible negative side effects of blood transfusion. Therefore, for this question a large observational study might be more appropriate to start with. However it should be kept in mind that observational studies are quite limited in their causal inference. It would be ideal to perform a double-blind study, but this might be unachievable because of the nature of delirium. To perform the best possible observational study, it is important to include information on the right confounders like severity of illness and other risk factors (such as blood loss for both delirium as anemia). It is also very important to consider timing of blood transfusion as to delirium and confounders. Therefore, there should be different study designs for transfusion as a prevention and as a treatment option for delirium. For both designs, delirium and hemoglobin levels should be assessed pre-randomization and at least daily afterwards. Other precipitating

factors and predisposing factors, like blood loss, hemoglobin level, and severity of illness should be taken into account.

To study the effect of blood transfusion on delirium incidence, well defined groups of patients (transfusion/no transfusion) should be included. Patients with delirium onset before transfusion should be excluded.

To study blood transfusion as part of the treatment of delirium, comparable groups of patients with delirium and anemia should get different treatment options for anemia and should be compared with each other. There should be an intervention group with patients receiving transfusion and control groups in which patients receive no transfusion. Outcome measures could be delirium duration and delirium severity.

In these examples, timing is considered by excluding patients with delirium to study the effect of blood transfusion on delirium incidence, and by including only patients with delirium and anemia (who did not get blood transfusion before the onset of delirium) while studying the effects of blood transfusion as treatment for delirium.

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SUPPLEMENTAL MATERIAL

Supplemental Appendix 1. Search Strategy

Anemia*[TiAb] OR anaemia*[TiAb] OR anemic[TiAb] OR anaemic[TiAb] OR "Anemia"[Mesh] OR "Blood Transfusion"[Mesh] OR transfusion*[TiAb] OR Red blood cell transfusion*[TiAb] OR Erythrocyte transfusion*[TiAb] OR Vitamin B12[Tiab] OR Vitamin B 12[TiAb] OR "Vitamin B 12"[Mesh] OR Cyanocobalmin[TiAb] OR Cobalamins[TiAb] OR Cobalamin[TiAb] OR Eritron[TiAb] OR "Folic Acid"[Mesh] OR Folic acid[TiAb] OR Folate [TiAb] OR Vitamin B9[TiAb] OR Vitamin M[TiAb] OR Pteroylglutamic Acid[TiAb] OR Folacin[TiAb] OR Folvite[TiAb] OR "Iron Compounds"[Mesh] OR Iron compound*[TiAb]

AND

Delirium[TiAb] OR "Delirium"[Mesh] OR deliri*[TiAb] OR acute confus*[TiAb] OR acute organic psychosyndrome[TiAb] OR acute brain syndrome[TiAb] OR metabolic encephalopathy [TiAb] OR acute psycho-organic syndrome[TiAb] OR clouded state[TiAb] OR clouding of conscious*[TiAb] OR exogenous psychos*[TiAb] OR toxic psychos*[TiAb] OR toxic confus*[TiAb] OR obnubilat*[TiAb]

Supplemental Table 1. Quality Assessment

Study (author and year)	1. Well-defined study groups	2. Selection bias adequate excluded	3.Exposition well-defined and adequate method of examination of the exposition	4. Outcome well-defined and adequate method of appraisal of the outcome	5. Outcome defined blind before knowledge of the exposition	6. Good follow-up	7. Adequate exclusion of selective loss-to-follow-up	8. Most important confounders or prognostic factors are known and taken into account in study design and analysis	9. Results of the study are valid and applicable
Behrends 2013[1]	Yes	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Uncertain
Beliaev 2012[2]	Yes	Yes	No	Unclear	Yes	Unclear	Yes	No	No
Bucerius 2004[3]	No	Unclear	No	Yes	Unclear	Unclear	Unclear	No	No
Fan 2014[4] [a]	Yes	Yes	No	Yes	Unclear	No	Yes	No	No
Gokgoz 1997[5]	No	Unclear	No	No	Unclear	Unclear	Unclear	No	No
Gruber-Baldini 2013[6] [a]	Yes	Yes	No	Yes	No	Unclear	Yes	No	No
Kawaguchi 2006[7]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	No
Kazmierski 2010[8]	Yes	Yes	No	Yes	Unclear	Unclear	Unclear	No	No

Study (author and year)	1. Well-defined study groups	2. Selection bias adequate excluded	3.Exposition well-defined and adequate method of examination of the exposition	4. Outcome well-defined and adequate method of appraisal of the outcome	5. Outcome defined blind before knowledge of the exposition	6. Good follow-up	7. Adequate exclusion of selective loss-to-follow-up	8. Most important confounders or prognostic factors are known and taken into account in study design and analysis	9. Results of the study are valid and applicable
Krzych 2013[9]	No	Yes	No	Yes	Unclear	Unclear	Unclear	No	No
Lee 2010[10]	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No	No
Lescot 2013[11]	Yes	Yes	Yes	No	Unclear	Unclear	Unclear	No	No
Li 2014[4]	Yes	Yes	No	Yes	Unclear	Unclear	Unclear	No	No
Marcantonio 1998[12]	Yes	Yes	No	Yes	Unclear	Unclear	Unclear	No	No
Mardani 2012[13]	No	Yes	No	No	Unclear	No	Unclear	No	No
McAlpine 2008[14]	Yes	Yes	No	Yes	Unclear	No	Unclear	No	No
Norkiene 2007[15]	Yes	Unclear	No	Yes	Unclear	Unclear	Unclear	No	No
Norkiene 2013[16]	Yes	Yes	No	No	Unclear	Unclear	Unclear	No	No
Roggenbach 2014[17]	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	No	No

Study (author and year)	1. Well-defined study groups	2. Selection bias adequate excluded	3.Exposition well-defined and adequate method of examination of the exposition	4. Outcome well-defined and adequate method of appraisal of the outcome	5. Outcome defined blind before knowledge of the exposition	6. Good follow-up	7. Adequate exclusion of selective loss-to-follow-up	8. Most important confounders or prognostic factors are known and taken into account in study design and analysis	9. Results of the study are valid and applicable
Sasajima 2000[18]	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	No	No
Schneider 2002[19]	Yes	Yes	No	Unclear	Unclear	Unclear	Unclear	No	No
Stransky 2011[20]	Yes	Yes	No	No	Unclear	No	Unclear	No	No
Vochteloo 2011[21]	No	Yes	No	Yes	Unclear	Unclear	Unclear	No	No
Yamagata 2005[22]	Yes	Yes	Yes	No	Unclear	Unclear	Unclear	No	No

[a] We performed an extensive quality check for these studies, because these are Randomized Controlled Trials, see text.

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